Sarcoidosis: A Hawaii rarity

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Sarcoidosis is so rarely seen in residents of Hawaii that it may not be considered as a diagnostic possibility. The differential diagnosis is more complex in Hawaii due to the presence of granulomatous diseases such as tuberculosis and leprosy. We present the first known case of sarcoidosis in a Hawaii resident together with an overview of the disorder.

Introduction

Sarcoidosis is a noncaseating, granulomatous disease which can affect virtually any organ system. A high percentage of patients undergo spontaneous resolution.

Sarcoidosis is common in certain areas of the U.S. and its clinical presentation is well known to most physicians there. The disease is rare in Hawaii and, therefore, may not be easy to diagnose at first glance. Complicating the diagnosis is the fact that other entities in the differential diagnosis are far more prevalent in Hawaii than on the Mainland. For instance, more cases of leprosy and Mycobacterium tuberculosis are seen in Hawaii, yet on the Mainland these diseases are rarely seen. In addition, granulomatous reactions to plants (particularly cactus and bromeliads), insects and sea urchins are commonly encountered in Hawaii and may simulate sarcoidosis.

We recently diagnosed the first case of sarcoidosis occurring in a long-standing resident of Kauai. The clinical findings were subtle and the diagnosis was not immediately obvious.

Case report

A 40-year-old woman presented to one of us (DJE) with small, somewhat painful nodules on the extensor aspects of both forearms that had been present for 4 months.

The patient was born in Portugal, where she had resided for the first 16 years of life; thereafter she lived in Mozambique. Later on, she emigrated to Kauai, Hawaii, where she has resided for the past 13 years.

The patient's past medical history was unremarkable. She was a para III, the last pregnancy having been in 1982, at which time she had undergone an elective bilateral tubal ligation. She had had a similar skin eruption on both forearms in 1988 which had resolved in 4 months. At that time, a chest X-ray was normal (Fig. 1).

The patient and her husband are farmers. Two months prior to her presenting herself to us, several red, tender nodules appeared on the anterior aspects of both lower legs. They disappeared in a few weeks. There were no other symptoms, specifically no respiratory difficulties and no visual complaints.

The physical examination was remarkable for several erythematous, flat-topped papules and plaques measuring 2 to 15 mm in diameter, arranged in an almost symmetric fashion on the extensor surfaces of both forearms. A barely visible circinate lesion measuring 8 cm in diameter was present over the anterior surface of the lowermost portion of the right leg.

A 3 mm punch biopsy of one forearm lesion revealed closely-packed, noncaseating epithelioid granulomas confined primarily to the upper dermis (Figs. 3, 4). The granulomas were bordered by a moderate lymphocytic infiltrate. A few multinucleated giant cells were present, including a rare Langhans cell. Birefringent particles were not identified under the polarizing lens. Fungal elements were not identified with the PAS stain and the AFB stain was negative. These findings were interpreted as consistent with sarcoidosis. However, neither leprosy nor a foreign body reaction (including to cactus

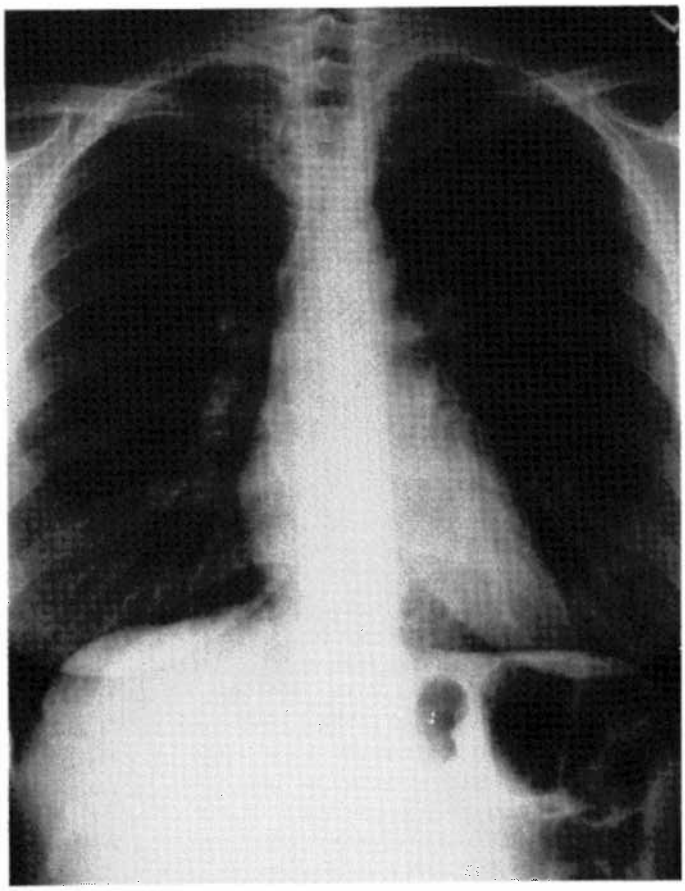

Fig. 1 Normal baseline chest X-ray, 1988.

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and similar plants, sea urchins, and insect bites) could be ruled out by histologic methods alone.

A chest X-ray revealed prominent, left hilar adenopathy and possible right hilar adenopathy as well (Fig. 2). Pulmonary function tests were normal; sputum culture was negative.

Laboratory studies (including calcium), urinalysis, and CBC were all within normal limits. Angiotensin Converting Enzyme (ACE) was 10.4 activity units (normal 2.0-7.5).

The patient was diagnosed as having sarcoidosis and no specific treatment was offered due to the mild presentation. The lesions on her lower extremities were diagnosed as erythema nodosum. At the time of this report, the skin lesions are resolving.

Discussion: Sarcoidosis

Our patient demonstrated a mild form of sarcoidosis which affects one-quarter to one-third of patients with this disorder; they often have with constitutional symptoms that may include cough, dyspnea, arthralgias, uveitis and a variety of skin lesions. A further one-quarter of patients, especially those on the Mainland, are asymptomatic, the disease having been discovered on routine chest X-rays. In our opinion, this subset may well be even larger, since many so afflicted obviously never visit a physician because they have no constitutional complaints.

The remainder of patients have a more insidious onset that develops over a period of months. This group is more likely to develop chronic disease with subsequent severe pulmonary and other organ damage.

It is quite likely that our patient was exposed to the putative agent (or agents) of sarcoid before moving to Hawaii, and that initiated sarcoidosis after a latent period of at least 13 years. Speculation concerning this activation process could center on poorly understood immunologic and/or genetic mechanisms. A further unknown factor acting as a hapten may have aided in the recognition of the dormant antigen by the patient's reticuloendothelial system. Or, it is possible that this new factor — or even the offending agent itself — was genetically transcribed, its coding system having been unlocked by an unknown environmental stimulus.

Epidemiology

The highest incidence of sarcoidosis is found in northern Europe and in North America. Sweden has the highest incidence of any country, at 64/100,000; however, according to autopsy studies, the true incidence may be 10 times higher[1].The incidence in the U.S. is 11 to 40/100,000, the highest being among Blacks in the Southeast. Parts of Africa and Japan also show a relatively high incidence. Sarcoidosis is rare in southern Europe and in southeast Asia.

In the U.S., Blacks are affected 10 to 17 times more often than Whites. Black women are affected twice as often as Black men, but the sex ratio in Whites is approximately equal. The disease is most common in the 3rd and 4th decades of

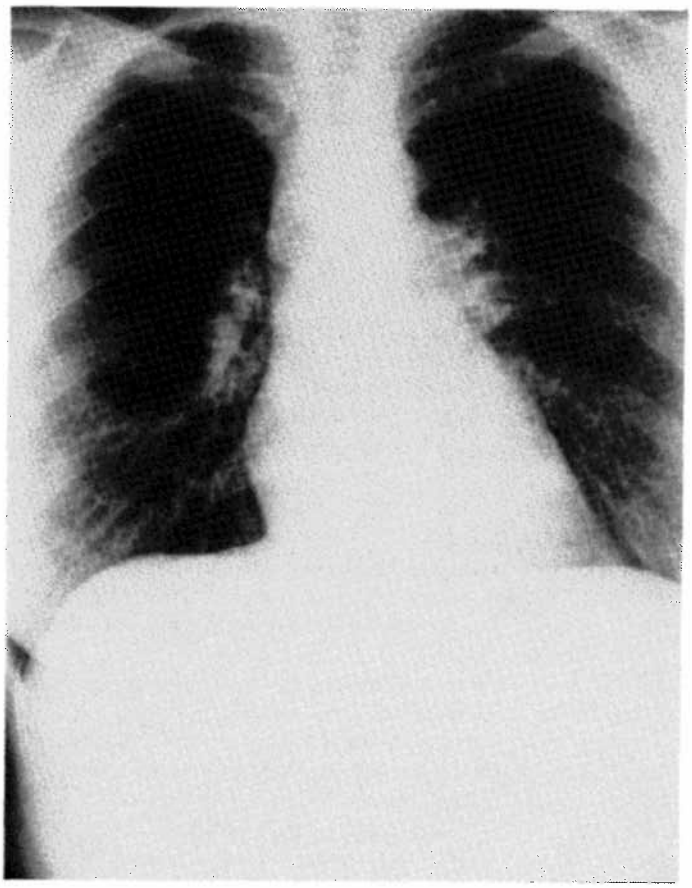

Fig. 2 — Left hilar adenopathy with possible right hilar adenopathy. Chest X-ray, 1990.

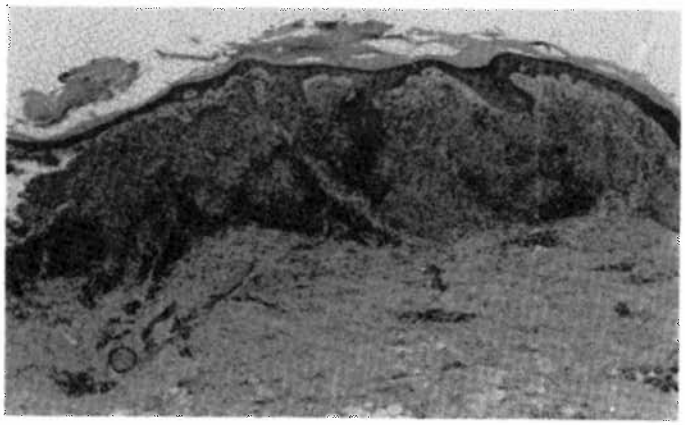

Fig. 3 — Skin biopsy demonstrating granulomas in upper dermis. Low power. H & E stain.

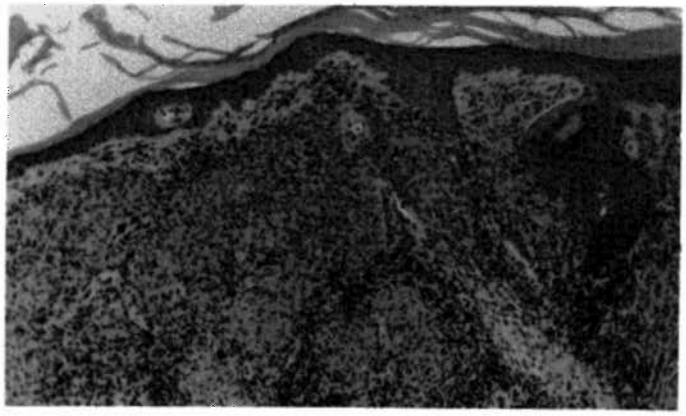

Fig. 4 — Skin biopsy. Mid power. H & E stain.

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life. An increasing number of familial cases are being noted, most frequently brother and sister[1].

Etiology and pathogenesis

Extensive studies so far have not elucidated an etiologic agent for sarcoidosis[1]. Many agents have been postulated as to the cause. These include Mycobacterium tuberculosis, Mycobacterium leprae, atypical Mycobacteria, a variety of viruses, fungi, inorganic agents and chemicals; however, the data are inconclusive.

Whatever the inciting event, the histopathogenesis of sarcoidosis suggests an immunologic basis[2]. It is postulated that an unknown antigen (or antigens) is recognized by a macrophage/histiocyte, which then stimulates the proliferation of helper T4 lymphocytes, that in turn stimulate B-lymphocytes to proliferate. The end-result is a granuloma composed of epithelioid histiocytes bordered by T-4 lymphocytes.

Clinical manifestations

Ninety percent of patients with sarcoidosis have an abnormal chest X-ray but only 5 to 15% develop serious pulmonary disease[2]. Overall, approximately 50% of patients have respiratory symptoms such as a dry cough, chest pain, shortness of breath, rarely hemoptysis. Less than 2% develop a pneumothorax. Intraparenchymal pulmonary granulomas have a predilection for the peribronchial, subpleural and interlobular septal connective tissues. Progressive disease with fibrosis is an interstitial process.

The skin is involved in 20 to 35% of cases[4]. A great variety of skin lesions have been associated with sarcoidosis; the most common are plaques, maculopapular eruptions, subcutaneous nodules, erythema nodosum and lupus pernio. The first 3 categories are ubiquitous in distribution. The papular form is most frequently located in the periorbital region, where it may simulate granulomatous rosacea. Erythema nodosum occurs in up to 25% of patients and may be the initial symptom. It is most commonly located on the anterior aspects of the lower legs and presents as tender, erythematous, or violaceous nodules. Most patients with sarcoid and erythema nodosum have a shortened disease course, with early spontaneous resolution. Those with Lofgren's Syndrome (a complex of erythema nodosum, bilateral hilar adenopathy, together with possible joint symptoms and uveitis) have an excellent prognosis. In one study, cases with erythema nodosum, acute arthritis and hilar adenopathy resulted in complete resolution of sarcoidosis in 85%, 83% and 73% of patients, respectively[5]. Sarcoid skin lesions have been reported in skin scars (including keloids) and in skin damaged by trauma, infection and radiation.

The eye is involved in 25 to 50% of patients with systemic disease[4]. The most common symptoms are blurred vision, tearing, and photophobia. Granulomatous uveitis is the most common eye lesion; approximately 75% of these patients have anterior uveitis and the remainder have posterior uveitis. The clinical course may be acute or chronic. Heerfordt's Syndrome (uveoparotid fever) consists of uveitis, parotid gland enlargement and facial nerve palsy. Conjunctival involvement is the second most common ocular finding and can lead to keratoconjunctivitis sicca. Eye involvement can be serious, leading to adhesions between the iris and lens, cataract formation, glaucoma and blindness.

The peripheral lymph nodes are involved in 50 to 75% of patients; most commonly the cervical, axillary, epitrochlear and inguinal nodes[3]. It is important to remember that sarcoid-like granulomas may occur in lymph nodes that drain a nearby malignant tumor. The spleen can be involved in up to 60% of patients, but symptoms occur only in the 15% of patients who demonstrate splenomegaly[3].

Liver biopsies have indicated involvement in 60 to 90% of patients[2]. The periportal regions are the most often affected by the granulomas. Cholestasis is rare, yet mild elevations of liver enzymes (alkaline phosphatase and serum bilirubin) are not uncommon.

Neurologic findings are present in 5% of patients[3]. Space-occupying granulomatous lesions of the cerebrum may cause confusion, seizure activity, hydrocephalus or hemiparesis. These mass lesions are most common at the base of the cerebrum and can elicit symptoms and signs related to derangement of the hypothalamic-pituitary axis. Chronic aseptic granulomatous meningitis has been recorded. Cranial and peripheral nerves are frequently involved, whereas spinal cord involvement is rare.

Cardiac symptoms are present in 5% of patients[1]. At autopsy, 27% of patients with systemic sarcoidosis have cardiac granulomatous lesions. The most common cardiac symptom is an arrhythmia caused by granulomas in the septum and ventricles. Sudden cardiac death may occur, and at autopsy these patients are found to have massive fibrosis and granulomatous involvement of the myocardium.

Kidney involvement is rare. Renal disease is usually due to an alteration in calcium metabolism, not to granuloma formation.

Sarcoid granulomas of the bone marrow have been reported in 15 to 40% of cases, although their effects on hematopoiesis are minimal[2].

Diagnosis

The diagnosis of sarcoidosis is usually based on the patient's clinical presentation, the primary ancillary test being a chest X-ray which, in at least 25% of patients, may be the only evidence of disease. The classic findings of Lofgren's Syndrome are adequate for a diagnosis of sarcoidosis[4]. Of utmost importance is the demonstration of noncaseating granulomas which must be differentiated from the granulomas of tuberculoid leprosy and foreign body reaction. Biopsies of skin or accessible lymph nodes are the most obvious choice to verify the existence of granulomata. If these sites are not revealing, bronchoscopic biopsies may be considered. Ophthalmologic examination and pulmonary function tests should be performed on all patients. The traditional Kveim test is rarely performed at present because the extract is not available and it lacks specificity.

ACE may be elevated. Produced by the epithelioid histiocytes of the granulomas, it is not a specific marker for sarcoidosis and is elevated in many of the diseases that fall within the differential diagnosis of sarcoidosis[2,6]. Sarcoidosis is a well-known cause of hypercalcemia.

Two specialized tests include broncho-alveolar lavage and the Gallium-67 lung scan. These are used in centers that regularly see patients with sarcoidosis. Lavage is done to ascertain the preponderance of lymphocytes, the majority of which are T-4[1]. This may be of aid in differentiating sarcoidosis from

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allergic alveolitis in which there is also a marked increase in the lymphocyte population; however, these are T-8 (suppressor) lymphocytes[3]. The Gallium-67 scan will often display a diffuse uptake consistent with the interstitial disease process of sarcoidosis. However, the scan is not specific; it is expensive and exposes the patient to a significant amount of radiation[3].

Differential diagnosis

The early chest X-ray changes of sarcoid can mimic tuberculosis, lymphoma and metastatic carcinoma, as well as systemic fungal diseases, most notably histoplasmosis and coccidiodomycosis. More advanced lung disease demonstrates changes on X-ray similar to that of extrinsic allergic alveolitis, fibrosing alveolitis, histiocytosis, systemic lupus erythematosus, rheumatoid lung, scleroderma and tuberculosis. On chest X-ray the most advanced disease can be confused with tuberculosis, bullous emphysema, bronchiectasis and melioidosis[6]. Furthermore, berylliosis, asbestosis, the diseases caused by silica, talc, mineral oil, and certain drugs (methotrexate, cromolyn sodium) can produce granulomatous lung disease and evoke a granulomatous response in lymph nodes but rarely in the skin.

Certain infectious diseases, apart from those already enumerated, are likely to provoke a granulomatous response in lymph nodes alone. These include toxoplasmosis, infectious mononucleosis, brucellosis, chlamydia, pneumocystis carinii, tularemia, various fungi, all stages of syphilis, the fairly early stages of cat scratch disease and lymphogranuloma venereum. Granulomas may arise in the bowel and mesenteric lymph nodes in Crohn's Disease, Whipple's Disease, and infection caused by Yersinia enterocolitica. Malignant tumors may evoke a sarcoid-like response in adjacent lymph nodes.

Many of the aforementioned entities can also produce granulomas in the skin. Further causes of skin granulomas include insect bites, delayed hypersensitivity reactions, leprosy, acne rosacea, granuloma annulare, tertiary syphilis, and pricks by sea urchins and by plants with spikes.

Sarcoid arthritis may be confused with gout, acute rheumatic fever, tuberculosis, Yersinia enterocolitica arthritis, and rarely rheumatoid arthritis.

Treatment and prognosis

Treatment is initiated depending on the severity of systemic or organ disease[1,3]. Therapy is not required for patients who present with an incidental bilateral hilar adenopathy on chest X-ray but are otherwise asyptomatic. Likewise, those presenting with an acute onset with some or all of the manifestations of Lofgren's Syndrome rarely require treatment because 80% will experience spontaneous resolution in any case.

Of all organ systems, the lung is the most often involved and the disease activity must be assessed fully. In most cases, clinical examination, pulmonary function tests, and chest X-ray will be sufficient. The chest X-ray findings are classically divided into 5 grades: Grade O - absence of abnormal radiographic findings; Grade I - bilateral hilar adenopathy without involvement of lung parenchyma; Grade II - bilateral hilar adenopathy and parenchymal infiltration; Grade III - widespread parenchymal infiltration without hilar adenopathy; Grade IV - irreversible fibrosis with the formation of bullae[1]. Treatment must be initiated in patients with Grade II disease if they are symptomatic or if more specialized studies (Gallium-67 scan or broncho-alveolar lavage) in asymptomatic patients establish an increase in the activity of the disease process.

Corticosteroids are the drug of choice for most patients with pulmonary and extrapulmonary disease (uveitis, cardiac arrhythmias, neurologic lesions and arthritis). Chloroquine and hydroxychloroquine are occasionally efficacious in the various skin manifestations associated with sarcoidosis, in particular lupus pernio. Interestingly, both corticosteroids and chloroquine tend to lower high serum calcium levels by inhibiting the action of active Vitamin D on the gut and also by inactivating the compound itself. This in turn will reduce the urinary excretion of calcium and prevent stone formation.

The prognosis in sarcoidosis is good. However, in perhaps 15% of patients the disease follows a chronic, persistent or recurrent course. Death directly related to sarcoidosis occurs in up to 6% of patients[4].

Conclusion

Sarcoidosis, a common disease in the U.S. and various parts of Europe, is very rarely encountered in Hawaii. Most physicians here have never seen a case in our state. Diagnosis may be difficult, and in fact may not even be considered. Both tuberculosis and leprosy can present with granulomatous skin lesions remarkably similar to sarcoidosis[2,7,8].

Skin involvement by either tuberculoid leprosy or sarcoidosis often cannot be differentiated, clinically or histologically one from the other. However, lepromatous leprosy usually presents with few or no granulomata, and macrophages tend to be packed with acid fast mycobacteria. Even so, the skin lesions of lepromatous leprosy can be difficult to differentiate clinically from sarcoidosis because they tend to present in the form of symmetric and bilateral plaques, nodules, or papules; erythema nodosum-like lesions may appear during reactional states[8]. Hypaesthesia is usually present in the skin lesions of tuberculoid leprosy yet not in those of sarcoidosis. Additional problems are encountered in distinguishing the 3 intermediate forms of leprosy: Borderline tuberculoid, borderline, and borderline lepromatous leprosy. In these situations, both the clinical and histologic appearance of the involved skin may be an exact replica of sarcoidosis.

In summary, we have described the first case of sarcoidosis to be reported from Hawaii. Undoubtedly, others have been seen but have not been documented in the medical literature. With the ever-increasing influx of residents to Hawaii from endemic areas, more cases of sarcoidosis are bound to be seen by physicians in the state.

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